down by a factor of ten or a factor of one-third? What is going to be acceptable? I can't imagine--I may be stupid but I can't imagine if you operated on patients for a refractive exchange that you are still not going to get a percentage of complications. They are not going to come out complication-free.

DR. WEISS: Right. Dr. Bressler?

DR. BRESSLER: I am going to echo what Allen said, and that is that when you already have good vision and a clear lens, having macular edema at the level of 0.3 percent might be the most that the subject could possibly comprehend and we were willing to accept a retinal detachment rate of that. I am somewhat comfortable accepting that as the macular edema rate that we want to be able to identify.

DR. WEISS: So, you would like the macular edema rate for three years to be what? This is the one-year rate for cataracts. What would you like for clear lens extraction?

DR. BRESSLER: I am still okay with 0.3 percent because in that case, again, it is going to happen almost all in the first year and you are not going to have people who then develop it additively

in the second or third year.

DR. WEISS: So, at least we have a comment on one of them of a 0.3 percent on macular edema. We are going to have Dr. Grimmett and then Malvina.

DR. EYDELMAN: Perhaps I can make it a little simpler. If we are talking about a three-year study for 300 subjects, or so, the maximum detectable rate for cumulative adverse events would be 0.3. So, perhaps we could ask do you feel that a rate of higher than 0.3 would be acceptable because we can't really detect with any precision anything below 0.3 percent?

DR. WEISS: So, what you are saying is for any of these categories, would we want to be less stringent than we are for the cataracts? Would we want a higher rate than what is being reported for cataracts? Did I misunderstand?

DR. EYDELMAN: No.

MR. CALOGERO: These are the mean rates here. We worked the statistics off these rates. If you have a pupillary block of, say, 0.1 percent that is the mean rate. This is a historical grid. Your study fails at one percent. So, your minimal detectable difference then would be 0.9. So, at the 0.1 you are failing at one percent. I ask what

Malvina is asking is what would you find acceptable. With a three-year study with 300 subjects it would be 0.33. That 0.33 would correspond to a much lower actual mean rate. In your actual study you could have a rate up to 0.33 and it would not be detectably different from the rate of 0.1.

DR. BRADLEY: I think we have basically got the idea that we are sample size limited and if we are specifying very low rates on a particular type of risk, lower than the rate which is driving the sample size, then we are not ever going to establish that rate. We understand that.

DR. EYDELMAN: Correct. Perhaps we can just concentrate on a few on the list which are above one percent or 0.8 and above and wee how those should be adjusted.

DR. WEISS: So, we are really only talking about hyphema and everybody agrees that rate is too high in macular edema.

DR. EYDELMAN: And secondary surgical intervention.

DR. WEISS: Dr. Brucker?

DR. BRUCKER: So, the issue of macular edema is probably not correct because it is based

on prior literature, extracapsular procedures, etc. So, it is probably much lower to begin with because these are 1980 data through 19-something. So, phacoemulsification posterior chamber IOL has a much lower rate. You are asking us what rate is it or what should it be. Neil is an authority and has written a couple of papers. Where should it be in 2002?

DR. BRESSLER: It is still, unfortunately for the cataract surgeons, around one or two percent.

DR. WEISS: So, what rate would you like--

DR. EYDELMAN: Our unofficial revision showed 1.5 percent.

DR. WEISS: If the unofficial revision is 1.5 percent, would everyone feel comfortable leaving it at 1.5 percent for a clear lens extraction?

DR. BRESSLER: As an acceptable risk? Is that the question?

DR. STARK: You are talking about cumulative or persistent?

DR. EYDELMAN: Well, 1.5 was for cumulative at one year. You are absolutely right, now we are talking about a three-year study.

Perhaps a persistent macular edema of 0.5 in this grid--what should it be for clear lens extraction? Or, we can ask what is the cumulative macular edema over three years. They are two different questions.

DR. WEISS: Dr. Stark?

DR. STARK: I would say persistent at 0.5 at the end of three years would be the maximally acceptable rate.

DR. EYDELMAN: So, that high is acceptable?

DR. STARK: It can be lower.

DR. WEISS: Dr. Mathers has pointed out it is going to be that high so it would have to be acceptable because basically it is the same procedure and Dr. Grimmett is agreeing. Dr. Bressler, and then I would like to move on from that. Yes, Dr. Bressler?

DR. BRESSLER: My question is in reference with what Dr. Rosenthal said, and that was, you know, what are we going to accept? And, these are individual events again. Is there any sort of guide that is needed, required or recommended in terms of if you add up all the adverse events that could occur, because you have persistent edema,

plus retinal detachment, plus something or other?

DR. EYDELMAN: For IOLs we have not designed studies like that. We have criteria like that under LASIK studies but we have never done IOL studies in such a way.

DR. BRESSLER: For a patient who otherwise has normal vision except for their presbyopia, this is more analogous to LASIK than to the IOL so I would suggest you consider those.

DR. WEISS: I am in a hundred percent agreement with Dr. Bressler. I think where we are going to have to be moving is having a hybrid between cataract IOL and refractive surgery because really this is a medical procedure, whatever, that has been done for people who have lost best corrected vision but it is being done for refractive purpose. So, I think we have to have grids more similar to those we have for refractive surgery patients.

DR. EYDELMAN: So, if I can challenge you further then, can you recommend a cumulative acceptable adverse event rate for a three-year study?

DR. BRESSLER: What was it in your refractive surgery ones?

DR. EYDELMAN: Those aren't three-year studies.

DR. BRESSLER: What was it? One year?

DR. WEISS: One-year study.

DR. BRESSLER: Better people than I thought about that for a long time--

DR. ROSENTHAL: Five percent--

DR. EYDELMAN: It was five percent but that included microkeratome so it was a combination.

DR. WEISS: So, we had a five percent adverse event for one year in LASIK.

DR. ROSENTHAL: Correct.

DR. WEISS: So, would anyone be willing to come up with what percent should be for visually significant adverse events or what type of adverse events would you suggest?

DR. BRESSLER: Well, it would be hybrid. It would mainly be driven by things that affect visual acuity.

DR. WEISS: Should there be a similar one year for this?

DR. BRESSLER: Cumulative, yes, and that seems a little high to me for this but I think that is because we are talking about more visually

significant events than what you suggested from the LASIK.

DR. ROSENTHAL: Correct.

DR. STARK: And also for refractive, Neil, you can't have more than a certain vision loss, and I can't remember what that is, but that should be tied in with it. Vision-threatening complications are what we want to get.

DR. WEISS: We don't have the refractive table in front of us but I am hearing sentiment, and I certainly have that sentiment, that this study should be basically looked at in addition in the same way that we looked at our refractive surgery studies because this is a refractive surgery indication, and Dr. Mathers seems to agree with that. Do you need anything else from us on this? Hyphema, did you need that from us? I think that should be a fairly trivial rate. Do you want to throw out a rate, Mike? Dr. Rosenthal?

DR. ROSENTHAL: You are talking about we have to compare this, if I am not mistaking you, to two guidances, one is the guidance related to the surgical procedure; the other is the guidance related to refractive surgical procedure. Is that right?

DR. WEISS: I think that is what was being suggested by Dr. Bressler, the reason being, as he points out, these people are coming in with normal best corrected and they want to know--

DR. ROSENTHAL: I understand.

DR. WEISS: --what their cumulative effect is. If that is fine with the agency, we are going to go to 5 C), do additional adverse events need to be collected? If so, what should their acceptable rates be? I think one additional one is just looking at it cumulatively, looking at it another way. Dr. Brown?

DR. BROWN: Loss of best corrected visual acuity.

DR. WEISS: So, loss of best corrected visual acuity.

DR. ROSENTHAL: That is part of refractive surgical guidance.

DR. BROWN: Okay.

DR. WEISS: If there are any other ones on the refractive surgical guidance that are not coming to mind, I think those would have to be considered by the agency as far as what would be relevant to this. Dr. Brucker?

DR. BRUCKER: I assume that corneal

decompensation, penetrating keratoplasty are automatically written in there.

DR. EYDELMAN: Yes.

DR. WEISS: Dr. Stark?

DR. STARK: One other thing, just to make sure that once a patient is entered into the study and they get to the operating room, if they have surgery and then they don't get an intraocular lens, that they are still continued in. So, there are going to be some situations where the patient doesn't get the implant after the incisions are made so we are going to have to come up with what is an acceptable rate of that too. Vitreous loss for example, you don't want to lose that patient from the study and say, well, that didn't happen; that wasn't part of it.

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: Actually, that comes into the definition of enrolled and once the surgical procedure begins that patient is considered enrolled and, therefore, any adverse events get captured regardless of whether the device was implanted or not.

DR. WEISS: Dr. Stark?

DR. STARK: You know, in the original IOL

studies we didn't have capsule rupture or vitreous loss because we assumed there would be no lens implants, and there were. So, you want to make sure that if the capsule is ruptured or there are surgical complications that these be recorded, especially if the lens is implanted with a vitrectomy. We would want to be able to capture that information.

DR. EYDELMAN: That is actually all on the current ISO forms.

DR. BROWN: Can I just add one item?

DR. WEISS: Dr. Brown?

DR. BROWN: This may be putting a hypothesis out before we really have strong data but one issue is in replacing the crystalline lens in young patients who are going to have to have this for many years, and does the lack of the properties of the crystalline lens promote the progression of retinal draws in patients who may likely develop AMD later in life? So, you know, it might be worthwhile in the post-marketing study to have a fundus exam and five years may not be long enough but it certainly would be worth at least documenting the fundus appearance for long-term adverse effect.

DR. ROSENTHAL: Is that accepted, Dr. Brown?

DR. BROWN: No, that is what I am saying, it is a hypothesis before we really have data for that. It is just something to think about.

DR. WEISS: Question 6, FDA believes that all multifocal IOLs' safety and efficacy profile will have to be established in a cataractous population prior to initiation of a clinical trial in a non-cataractous population. Multifocal IOL performance cataractous population will, therefore, be known for all tests and sub-studies outlined in ANSI draft standard for MIOLs. Which sub-studies do you recommend for inclusion in the clear lens extraction protocol for evaluation of performance in this non-cataractous population?

One thing that I am going to ask--this is sort of similar to the refractive surgery population--I would like to know visual acuity postop in terms of what percentage of people are wearing glasses. I don't know if that would fit in here or fit somewhere else but is that going to be a criterion in these studies? Because if 40 percent or 50 percent are still wearing glasses, obviously, it didn't have the impact that one would

hope.

DR. EYDELMAN: That would go under subject survey. Under the study those are all the evaluations done on all subjects.

DR. WEISS: I see.

DR. EYDELMAN: So, we are moving to the sub-studies. That implies that the subject survey would be repeated.

DR. WEISS: So, that would be under F), "others" in terms of the--

DR. EYDELMAN: No, it would not be a sub-study. It would be in the study.

DR. WEISS: It would be in the study as a subject study. Dr. Brucker?

DR. BRUCKER: Can I ask two questions? One, why do you make the assumption that you make without having any data to back it up? Second, if this study shows that there is no increased complication rate, why can't multifocal IOLs be judged on their own merit later on down the line without having to be in cataractous patients?

DR. WEISS: What assumption are they making, just for the first one?

DR. BRUCKER: If you can back up on the right side? The FDA believes that all multifocal

safety and efficacy programs will be established in cataractous patients. And, I am asking why are you making the assumption--because it says "we believe that..." and I am asking you if this trial now shows that there is no difference and there are no complication rates that are not predicted, etc., etc., etc. why should you do that?

DR. EYDELMAN: Generally, when we evaluate a brand-new device we start out with placing it in the population where the safety and risk benefit are different. In other words, As we try to place it in a subject that will benefit the most and have the least risk.

DR. BRUCKER: So, if this trial--I am playing devil's advocate--if this trial shows that there is no increased risk and the patients are benefiting, then anybody who submits an application for an intraocular multifocal lens in the future should be able to put it in either population.

DR. EYDELMAN: Well, we don't have a trial yet so today we are discussing the status as of today.

DR. BRUCKER: You put that slide up; I didn't.

DR. WEISS: Dr. Rosenthal?

DR. ROSENTHAL: These are Class 3 devices so that any time a new one comes on the market it has to be studied. You can't find a substantial equivalent to an existing IOL.

DR. BRUCKER: Right.

DR. ROSENTHAL: You have to study it.

DR. BRUCKER: Right, so I am saying--

DR. ROSENTHAL: And if you are going to study it, I think the agency has taken the tack that you should study it in a population that has cataracts first because we have well-established guidelines for what is required for an IOL to get through the process. Now, if a company wants to come here and study it in a non-cataractous population, they are welcome to do so but we can't allow them to put it on the market for both populations until they have certainly studied it for one, and actually because the indication is totally separate. As you can tell, it has taken up a day's worth of discussion on the issues related to this one. We would not allow them to get the second indication without a study. Have I made that clear in my unclear way?

DR. BRUCKER: That is a different explanation. It is an explanation of why it is

believed.

DR. WEISS: So, we are fine on that. We are going to go on to Dr. Bradley and what I am going to ask is, anyone who decides to answer this one, if you can indicate whether you want any of those sub-studies or any other sub-studies.

DR. BRADLEY: I think Dr. Brucker's comment relates to the issue of the risk associated with lens extraction surgery and is quite correct I think. There would be no need to employ a cataractous group. I think the issue at hand though is with each novel, potentially multifocal lens which can have its own specific risk and efficacy problems, because of that unknown presumably the FDA has chosen to employ a group for which the risk/benefit ratio is different. It is not the surgery.

DR. WEISS: Thank you, Arthur. Now, for the second part of your answer, do you have any comments on that, succinctly put?

DR. BRADLEY: Could you give me a minute?

DR. WEISS: I will give you a moment. Dr. Brown and then Dr. Mathers.

DR. BROWN: For efficacy I would like to see a reading speed under functional performance to

see that you have actually improved that.

DR. WEISS: Is there such a study that is done in terms of reading speed?

DR. BROWN: There are validated tests that use standardized text format, placement, lighting.

DR. WEISS: Dr. Rosenthal?

DR. ROSENTHAL: And the reason we are asking this, as has been alluded to before, you are taking patients with, hopefully, 20/20 vision clear lenses and you are taking them out and putting in multifocal lenses. Do you want to see is there a drop in contrast sensitivity? I think obviously fundus visualization we would include in all of them just because it is good medicine. But, you know, it is not taking the cataractous lens where we don't require--well, we require sometimes these sub-studies but you are taking someone who has a clear lens or a peripheral cataract, or something, and are there changes that occur that you want to inform the patient about that may be of importance to both them and to the doctor?

DR. WEISS: Dr. Brown, would you want to exclude any of these? Would you want to include all of them? I think most of us would say fundus visualization. You need contrast sensitivity, I

would think. Your well-taken point of at least one aspect of looking at functional performance. Endothelial cell evaluation has come up before so I think there would be agreement on that. For defocus curves I would defer to everyone else on the panel. Is there anything here that you wouldn't want or anything in additional that you would want? You would go along with that? Dr. Mathers, then Dr. Ho, then Dr. Brucker.

DR. MATHERS: I would like to see glare testing and I would also like to have recorded symptoms of halos and symptoms of glare, not glare testing.

DR. WEISS: So, I think we are going to need a survey which has the subjective symptoms of those phenomena that we know you can get with these sort of IOLs, in additional to the refractive type of questions that you would ask as far as what sort of activities can you do without your glasses. Dr. Ho?

DR. HO: Ralph, can you just explain a little bit more? Are you saying that fundus visualization is just perfunctorily put on any IOL follow-up? You may not need to do a study. It is harder to see the fundus through multifocal IOLs.

DR. ROSENTHAL: Well, we know that.

DR. HO: Okay.

DR. ROSENTHAL: But we have to know whether it is so hard that if they do get a problem in the back of the eye it won't be able to be dealt with.

DR. WEISS: That is why we have retina specialists. Dr. Maguire?

DR. MAGUIRE: I don't if anybody has given any thought to this, but it is not just seeing in the back of the eye; it is doing laser treatments to the peripheral retina when they develop holes and retinal detachments and everything else later on, and also visualization. This is a real mixed group here. I mean, we have an Array lens which has degraded optics to get increased depth of field. We have the newer lens that has a very small diameter and you are going to have to try and get your lens around that to get out in the periphery. I don't know if it is possible or whether it is within agency boundaries but I would like to see some good studies on how laser energy is delivered to the peripheral retina on these different types of intraocular lenses because that is a real public health issue too.

The other thing is for defocus curves in lenses that suggest that they create some portion of the presbyopic correction through accommodation, I think a Hartman Schack analysis at a place like Dr. Williams' place in Rochester, New York or something like that to actually prove that they are getting their effect from accommodation and not from increased depth of field.

DR. WEISS: We don't really have to have an improved mechanism; we just have to have improved results.

MR. CALOGERO: Can I clarify a little bit here? All this testing here would already have been performed on, say, a multifocal lens in the cataract population. The question is now you are simply changing the population. You have a younger population that didn't have a cataract. Is there any expectation that the results in any of these tests may be different simply because you are putting it in this new population? We don't want to repeat all these tests if they are not necessary.

DR. WEISS: Dr. Maguire?

DR. MAGUIRE: Functional performance certainly because you are taking patients with

cataract initially who already have decreased optical function. Now you are taking people that are normal and exposing them to lenses that sometimes have degraded optical performance to increase depth of field. Obviously, they may get a different response than the cataractous group.

MR. CALOGERO: We have already had the results from the functional test--

DR. WEISS: For the cataractous population. I think Dr. Maguire knows that.

DR. MAGUIRE: But you are starting from a different baseline.

DR. WEISS: I have heard the panel members sort of agree that at least functional performance should be repeated in this population. From what I understood that Ralph just said, fundus visualization is going to be repeated whether we say it should or not. Is that correct? That is going to be part of the protocol whether or not we recommend it? Yes, you can elucidate.

DR. EYDELMAN: If I can just clarify something, you mentioned about functional. You wanted an addition of reading speed and that is a separate issue and we all agree. But currently the testing that is recommended under functional is

driving simulation. So, what we are asking is if functional needs to be performed, then your recommendation is that the company does a second driving simulation to show the difference between preop and postop in this new population. That is specifically 6 A).

DR. WEISS: I personally would want that because these people came with presumably excellent best corrected visual acuity at distance preop and if we found that their functional for the driving simulation had decreased, that is something patients would want to know. With the cataractous population presumably it would improve. But here the best corrected at distance may not improve; it could get worse. Does anyone disagree with that? Dr. Bradley?

DR. BRADLEY: I am not disagreeing.

DR. WEISS: Okay. So, I think we all agree that functional performance, we want what is already being performed to be repeated in this population in additional to near vision functional performance, which was suggested to be reading speed.

DR. EYDELMAN: A second clarification, glare testing is part of contrast sensitivity.

DR. WEISS: Then do people feel that contrast sensitivity should get repeated in this population? I see nods and I see nods fairly uniformly so we want contrast sensitivity repeated again in this population.

Defocus curves, do people want that repeated in this population? I see definite no responses on that one. So, we don't have a lot of strong interest one way or another on defocus curves.

Fundus visualization, do people want that repeated in this population? One no and a question. Dr. Grimmett?

DR. GRIMMETT: Was that helpful in the original evaluation of some of these lenses in the cataractous population? Did that help you one way or the other?

DR. EYDELMAN: Well, we have only had one MIOL approved so far, and what was required of that MIOL is different than what is recommended currently in the ANSI. We had a specific small sub-study where they did more than just look but there was a lot of discussion on the ANSI and that is the current recommendation. Since this is now a population after clear lens extraction that is

going to be around longer that might need laser treatment, that might have RD, do we need something more specific than a general questionnaire for this population that will clarify visualization of the retina? That is where this is going, or hoping to go.

DR. WEISS: Dr. Ho?

DR. HO: There is no reason to believe that there is a difference between the clear lens group and the cataractous group, in my opinion. If you want to get to the next level, as Leo suggests, or maybe a couple of levels up in terms of doing studies of energy and things like that, I think that is a separate issue. I would argue those are interesting studies. I think they would be worthwhile studies but I am not sure that--as you have described it, we know that it is more difficult to see through them or to operate through them or to laser through them.

DR. WEISS: What about the question about vitreous adhesions in the younger population that are going to be the subjects here? Do any of the retina folks have concerns about that as far as fundus visualization? I see no. Dr. Brown and then Dr. Bradley.

DR. BROWN: In that original study did you look at the peripheral retina? Was that part of the fundus visualization or was it just macular? Do you know?

DR. EYDELMAN: It was the whole retina.

DR. BROWN: And it was graded on some sort of 1-4 kind of thing?

DR. EYDELMAN: I don't remember how much of it was discussed in the open public hearing.

DR. WEISS: Dr. Bradley and then Dr. Brucker.

DR. BRADLEY: Well, we finally go on to the issue of effectiveness of these lenses after talking about risk all day. I have several comments on that. First off, we are all aware that there are three ways you can provide near vision for presbyopia, in this case a lens that is inserted into the eye. One is that you can make them a little bit myopic. One is that you can aberrate the lens and give them increased depth of focus. Finally, you can actually have a lens that can change power, that is a truly accommodative lens. All three have been used. I think at one level, whatever study design is done, would be able to discriminate between those three techniques and

that is very important.

The one we are specifically talking about today is the multifocal because I think that is the first batch of lenses that are going to come through the FDA. The accommodative ones, we will see plenty of those soon I think. These multifocal lenses come with their own concern, that is, they provide improved near vision at the cost of degraded distance vision. So, it is essential that distance vision be monitored very carefully with these lenses.

It is very important to ensure that the issue of pupil size is examined in this patient population because in a highly aberrated eye the aberrations will have more and more impact as the pupil dilates. This, obviously, is particularly true for these patients at night. Therefore, for the issue of safety and visual function the most important issue to monitor is night vision at distance; is that compromised in these patients? That is the most critical situation.

The question was do we measure glare testing? That is one thought. Do we do night vision driving? First off, glare testing is a very poor technique for assessing night vision problems,

as you already know. You turn on the glare source, the pupil constricts, etc., etc. So, that doesn't work very well. Night vision driving simulations, the average night vision driving simulator is a very poor simulator of night vision. The reason for it is that if it is entirely computer based, the computer can generate about 100 to 1 range of intensities. The entire reason that you have night vision problems when you drive is that you are talking about millions to 1 intensity range in the environment, that is, dark road, very bright headlights. The typical night vision driving simulator cannot simulate that and that should be known and built into any study design. Try and get one that can accurately simulate the intensity range that is going to exist at night. So, I am very concerned about the large pupil, the night vision problem at distance.

We move on to the issue of near vision. How do you assess near vision? There really aren't any standard ways that are particularly good, in my opinion. I do like the idea of having a near reading test. In the end, that is what the patients want. They are all presbyopic, coming to their clinician because they can't read anymore.

So, I like the idea--whoever presented it--of doing a reading test. It is my personal experience, now becoming a presbyope--that the particular near test that is so critical is reading a low contrast text. Any parents who have children who play video cards will know all about this. It is 4-point type; it is very low contrast; and you simply can't read it unless you are well refracted at near. Likewise, patients trying to read prescription bottles where they have poor print.

Finally, I think the issue of near vision can be evaluated in a survey with assessment of spectacle use. I think a series of questions on that topic will help. Again, spectacle use under different circumstances--do you need your spectacles in a restaurant at night, dim light, trying to read the bill? That is when I need my reading glasses.

So, be aware that there are ways to assess near vision but they are not standard clinical tests, and I think those should be employed. Thank you.

DR. WEISS: Those are really excellent comments, Arthur, and I think your sort of directing these to what the issues with this

particular technology is going to be is a very, very important additional to this. Dr. Brucker?

DR. BRUCKER: Just a question, have fundus photographs ever been done as a sub-study?

DR. EYDELMAN: That was part of the original sub-study for the first MIOL but it is no longer recommended. So, if that is your recommendation that would be something additional.

DR. BRUCKER: As long as it has been done--

DR. EYDELMAN: Well, it was done for only one IOL. It is not going to be done for other MIOLs that are coming along.

DR. BRUCKER: That would be a mistake, but if this IOL has been reviewed then it doesn't need to be done.

DR. WEISS: Well, you can request that if the IOL has not had this done that it should be done. You could include that.

DR. BRUCKER: We have an aging population, macular degeneration first and angiography laser treatment. It ought to be known whether you can do a photograph through one of these things.

DR. EYDELMAN: How many subjects do you feel you would need to assess that?

DR. BRUCKER: Half a dozen.
DR. EYDELMAN: Originally we had a sub-study of ten.
DR. BRESSLER: You mean five that had it and five comparison?
DR. EYDELMAN: I think it was ten and ten.
DR. BRESSLER: That is fine.
DR. BRUCKER: That is fine.
DR. BRESSLER: You can tell very quickly I think.
DR. WEISS: So, what I hear is that we don't need fundus visualization because it has been done already but it would be helpful to know whether you can photograph these people. Dr. Brown?
DR. BROWN: But I do think that as each new technology comes out that that be replicated for visualization also. For the periphery is what I am particularly just curious about, whether they are going to get to the edge of this lens? Does it distort the view so much that you can't see?
DR. WEISS: Would you be satisfied though with, let's say, ten eyes or ten patients as well? So, it is a very, very small subset to look at the periphery and do photos to see if that would be

impaired by the IOL? Does that seem satisfactory to the retina folk among us?

Endothelial cell evaluation, is that something that we want to repeat in this group if it has been done in the cataractous population, that is fine?

DR. BRUCKER: I would say that if the flow of liquids, flow of aqueous and the dynamics in the eye is not thought to be detrimental or changed by the irregularity of the surface of the lens, then you don't have to do endothelial cell counts. But if you have a lens that shimmies and has a particular configuration that the physicists think may be causing current change in the eye, then you should look at it because you may lose endothelial cell count.

DR. EYDELMAN: I just want to clarify, there are no endothelial cell sub-studies in the regular MIOL. That was not on the list; that was an additional criteria.

DR. WEISS: This one was not performed before--

DR. EYDELMAN: Correct.

DR. WEISS: --so if you want it done, it would have to be done in this population.

DR. EYDELMAN: Correct.

DR. WEISS: Dr. Grimmett?

DR. GRIMMETT: I would be in favor of an endothelial cell sub-study even if the data exist in the cataractous population. You are looking at a different age range and you may have different endothelial dynamics, endothelial cell layers more robust in the young. You may find different things depending on the age range that you look at. I would be in favor of having an endothelial cell sub-study.

DR. WEISS: We are going to have one more comment by Dr. Smith. Then, if we are okay with the agency, we will go on to the next. Dr. Smith?

DR. SMITH: I would just echo Dr. Grimmett's comments and say it is very important to add that.

DR. WEISS: I would want that done as well in the post-market study.

DR. EYDELMAN: Wait a second, are you saying you want it in the pre- and post-market study? Because from what I understood in the discussion before, the post-market is going to be very large and it is going to be a yes or no.

DR. WEISS: Actually, I will withdraw what

I just said. Any other studies that we want aside from the survey for which Dr. Bradley had mentioned a bunch of things?

DR. STARK: Did we decide that vitreous examination and documentation was too difficult to do?

DR. WEISS: We decided that there would be five or ten patients that would have periphery of the retina as well as photographs done.

DR. STARK: I am talking about documentation of the status of the vitreous and vitreous--

DR. WEISS: I don't think that was going to get done. Dr. Brucker?

DR. BRUCKER: I don't think it is very practical. OCT would be great but only within several millimeters of that surface, it is probably not worthwhile.

DR. WEISS: So, that won't get done. If agency is fine, we will go on to question 7. The only current performance efficacy endpoint for aphakic posterior chamber IOLs, FDA grid, is postoperative best corrected vision of 20/40 or better in 92.5 percent of the subjects. Is this applicable to non-cataractous eyes undergoing clear

lens extraction for the correction of presbyopia? Dr. McMahon?

DR. MCMAHON: No.

DR. BRESSLER: I agree.

DR. WEISS: Dr. Bressler agrees. So, I assume you want higher criteria. Do you want from us what the higher criteria are or is all you need to know that that is not going to be sufficient for this population?

DR. EYDELMAN: Well, you have decided to have an inclusion criteria of 20/20 so it is up to you whether you want to set an efficacy endpoint of maintaining BC of 20/20 post surgery or not.

DR. STARK: Don't we have criteria already for the refractory surgery protocols? It would seem to me like you would keep those same criteria and you would agree that a few may lose one or ten letters, or whatever, but after a while we should set a standard similar to the refractive surgery protocol.

DR. WEISS: I would agree with that.

DR. EYDELMAN: The only criteria we have in the refractive is for UCVA and predictability. We don't have criteria for BCVA and that would be okay.

DR. STARK: I thought we had loss of--
DR. WEISS: It is one or two lines--
DR. EYDELMAN: That is safety; that is not for efficacy.
DR. WEISS: I see.
DR. EYDELMAN: It is an efficacy endpoint.
DR. WEISS: But what is the percentage for the loss of two lines or more BCVA.
DR. ROSENTHAL: It is one percent.
DR. WEISS: One percent? Then we are talking about 99 percent. If they were all starting out 20/20, it would have been 20/30 or better. Is that correct if you translate it over to efficacy?
DR. EYDELMAN: If you want to keep it as safety and not introduce efficacy in terms of BCVA, that is fine. You don't have to create additional criteria; you can stick with--
DR. BRADLEY: Let's keep it as safety.
DR. WEISS: Dr. Stark?
DR. STARK: If you look at it in efficacy you have to take into consideration the magnification of the myopes and the minification of the hyperopes. But I think we should have it as an efficacy issue also.

DR. WEISS: I think we also need a best corrected visual acuity standard and the question is what number do people want to come up with. You know, this is being done for refractive reasons and we wouldn't want too many people losing vision. Dr. Bressler?

DR. BRESSLER: I just want to confirm what people are agreeing to on the table. One, I do think it should be done for safety because the efficacy is going to be all the wonderful suggestions that Dr. Bradley has brought up. I just want to confirm that we are discussing that it is going to be a change in letters of ten or more, for example, because if you start at 20/12 as some of these people may, then if they go below 20/20 that is an adverse event.

DR. EYDELMAN: Right. As far as safety, we always talk about ten letters or two lines of BCVA loss.

DR. WEISS: Does the panel want to have efficacy including what your best corrected visual acuity is or not in this case? No? That was a no?

DR. WEISS: Dr. Brucker?

DR. BRUCKER: So, you are willing to take a 7.5 percent visual acuity loss of three lines--

DR. WEISS: No, I don't think anyone wants to use that. That is not going to be applicable. The question was is that applicable here and I think the consensus of the panel was that it is not applicable.

DR. BRADLEY: It is a safety issue, the issue of best corrected visual acuity, and always has been. Obviously this would be unacceptable for safety--

DR. WEISS: We are saying it is no good; we don't want it. We are just saying it has to do with the safety; it is not efficacy. We are going to be judging these efficacious in different modes. That is satisfactory to the agency and we will go on to B), are the predictability outcomes outlined in FDA's draft guidance for refractive implants applicable, 75 percent of eyes standard MRSE plus/minus 1.0 diopter, 50 percent with MRSE plus/minus 0.5 diopter and uncorrected vision, 85 percent with 20/40 or better. Is that applicable here?

DR. WEISS: Dr. Bradley?

DR. BRADLEY: A suggestion to FDA to perhaps update these data to the better of the new lenses that you have seen. These old standards may

be too lax.

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: There aren't for lenses. This is for refractive.

DR. WEISS: But I think we have to add to that near vision criteria.

DR. EYDELMAN: That is C), 7 C).

DR. WEISS: Is this sufficient for IOLs for distance and for refractive, plus/minus 1.0? Did you want to say something?

MR. MCCARLEY: Well, the only comment is I was going to ask you what are your guidelines for cataract lenses on predictability and so forth? I know this is more and this is the LASIK and phakic lens guidelines. There aren't any for regular IOLs.

DR. EYDELMAN: No, that is why I said the only efficacy endpoint for IOLs is BCVA.

MR. MCCARLEY: Exactly, that is my point.

DR. EYDELMAN: That is the distinction I was trying to make.

DR. WEISS: I think this also will have to change if we are doing higher myopic levels than what we are talking about because if these are going to be used for beyond what the LASIK

guidelines are, you can't apply the same levels if we are doing a very high myope. I don't think we are just in terms of the criteria that are set forth here. Walter?

DR. STARK: We need to add also uncorrected visual acuity and whether or not there is a drop in that. If we are taking plano patients for presbyopia and they are 20/20 we need to look at what percent of them are no longer 20/20 uncorrected afterwards.

DR. WEISS: Is that efficacy or safety?

DR. EYDELMAN: Change in UCVA would be efficacy--

DR. STARK: It would be efficacy; they could be corrected with glasses.

DR. EYDELMAN: BCVA would be safety and UCVA is efficacy.

DR. ROSENTHAL: Excuse me, let me have some idea of what the panel thinks should be the percentage of patients who have uncorrected visual acuity of something/something or better. If you are taking 100 patients that are 20/25 and 20/20 and 20/15 what percent of those do you allow to drop down to 20/40?

DR. EYDELMAN: Actually, it is the same

thing only a little bit twisted because you are taking essentially patients, many of whom will be UCVA 20/20 preop but the only postop criteria is that UCVA of 20/40 is a success. We don't have any UCVA of 20/20 as a success, as a set endpoint. Ultimately you can have 75 percent of your subjects 20/20 UCVA preop and 85 with 20/40 but only 50 20/20 so the UCVA went down but it would still be considered a success.

DR. WEISS: The thing is really what the criteria for the final percentage that need to be UCVA 20/20 is very dependent on who you are entering into the study. If 100 percent of those are emmetropes, then you might want a 95 percent 20/20--

DR. EYDELMAN: That is one question.

DR. WEISS: --if they are all minus 12 you are not going to have the same expectation. So, what we are going to tell you is going to be totally dependent on whom you are entering into the study. We could have them for different categories and say, you know, between plus 2 to minus 2 we have this expectation of UCVA; above minus 10 we have this expectation of UCVA.

DR. ROSENTHAL: That is what we would

like.

DR. WEISS: Dr. Maguire?

DR. MAGUIRE: I pass.

DR. WEISS: You pass? So, you would like from us somewhat of a grid, what we want the UCVA of 20/20 percentage to be dependent on the entry criteria of the patients?

DR. ROSENTHAL: Correct.

DR. BRESSLER: Adjusted for induced magnification of course.

DR. EYDELMAN: That actually comes into effect only at 15 diopters.

DR. WEISS: Does anyone want to give us--Walter, do you have any guidance as far as what you would want percentage UCVAs to be for various groups?

DR. STARK: I would have to think about it but it would depend on the starting point. You know, it is a safety/efficacy issue, where they started, but I would have to give it some thought. We could develop that for you, recommendations.

DR. WEISS: If we are dealing with low myopes, low hyperopes and emmetropes what would we be saying--yes?

DR. EYDELMAN: I am just trying to think

of a typical subject. Theoretically, they are going to have clear lens extraction because they don't want to wear glasses. If they still need to wear glasses for distance but don't need to wear them for near, would that be a typical subject? Even though it is correction of presbyopia, would somebody who needs glasses for distance and near be happy with wearing glasses only for distance but not near?

DR. WEISS: Dr. Brucker?

DR. BRUCKER: I think that this is an elective procedure for emmetropes or anybody with refractive errors and if you turned around and took a hyperope and made them a little bit more hyperopic, even though they didn't need reading glasses anymore, they would be really, really, really unhappy. So, I think that this number of 85 percent with 20/40 vision would be unacceptable.

DR. WEISS: What would you like the number to be?

DR. BRUCKER: Well, I think that you should be having an uncorrected visual acuity closer to the 20/20 and a percentage considerably higher. It should be a more predictable way of coming to a conclusion in these elective patients.

I don't do refractive surgery so I don't know what is the realistic expectation but I would be pushing 90 and 95 percent coming within 20/20 vision.

DR. WEISS: Dr. McMahon?

DR. MCMAHON: I wrote exactly the same thing and said 95 percent or greater equal to 20/25, 20/30 depending on the group entrance level. I think you need to be in that range. I don't know if it is realistic but--

DR. WEISS: So, we have Dr. Mathers, Dr. Bressler, Dr. Maguire and then Dr. Bradley.

DR. MATHERS: I think 95 percent should see 20/30 at least. That is certainly attainable. That is reasonable.

DR. WEISS: While we are going around, does anyone want to throw in their criteria for near vision because this is being done for presbyopes so if you are getting excellent uncorrected distance acuity vision but your near visual acuity isn't any good, then it sort of makes the whole thing pointless but I will ask the other people answering these questions to address that as well. Dr. Bressler?

DR. BRESSLER: I wonder if there is some way of turning it around, because of the example

you gave where the uncorrected visual acuity doesn't drop more than ten letters, for example, because it may be that someone is 20/20 with their glasses and they just want to get rid of their presbyopia, and they may be a success at near even though their distance still requires their glasses. I don't look at that as a problem, if that was 50 percent of the cohort, if they all solved what they were trying to do, that is, get rid of their presbyopia. If it is to correct both their presbyopia and their distance visual acuity, that is a different question and that is not what we are dealing with. So, I would propose to see if there is a way that it could be worded so that, again, it is a ten letter or more loss from their distant uncorrected visual acuity and their near uncorrected visual acuity.

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: If you were doing surgery for correction of near vision, having an efficacy of a drop of ten letters of near vision--

DR. BRESSLER: I took it better for near.

DR. STARK: He meant a gain, I bet.

DR. ROSENTHAL: He meant uncorrected distance and best corrected near.

DR. BRESSLER: That is correct.

DR. WEISS: Dr. Mathers?

DR. MATHERS: It is a little more complicated because most of these people have a little bit of monovision as well, and what they are really interested in is a binocular distance vision that is acceptable and a reading vision that is acceptable. That is usually 20/25 distance and J3 binocular, but the individual eye doesn't really matter to the patient. So, that is the reality of what they are really trying to get at and we can have relatively softer terms per eye as long as they get there together.

DR. WEISS: Dr. Hilmantel, did you have a comment? DR. HILMANTEL: Yes, you may want to consider some kind of target like 90 percent or 95 percent getting both distance and near of a certain level like 20/30, both simultaneously.

DR. WEISS: I am in agreement with you because the near hasn't been addressed and the near is the only reason that they are having this done. Dr. McMahon and then Dr. Bradley.

DR. MCMAHON: I would float a new target of 75 percent greater than or equal to J3 and 50

percent greater or equal to either J1 or J2, I am not sure which is the best there. I just think establishing a level for J3 is not good enough.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: It is worth considering that unlike the refractive surgeries that we have been looking at, the corneal ablative surgery, as you approach zero correction you are ablating this material, you introduce less error. In this particular surgery the error doesn't approach zero as the refractive error approaches zero. Add to that that we are talking about multifocal lenses, which are highly aberrated lenses, which must degrade vision to some degree, and you have an error for an emmetrope; you have a multifocal lens for an emmetrope and it seems to me that the emmetropic example that has been thrown around here is that they are all likely to have a significant decrease in their distance visual acuity and that is just the reality of this particular procedure.

A second point relating to near vision, I think that standard clinical tests, high contrast acuity, are likely to underestimate the problems experienced by patients at near, particularly with multifocal lenses and that is why I suggested a

reading task, preferably a low contrast reading task and preferably one in dim lighting would allow you to evaluate the actual near vision problems encountered by these patients.

DR. WEISS: I want to get back to the efficacy criteria that we are trying to skirt about here. We have a distance uncorrected visual acuity and we have a near uncorrected visual acuity. The distance uncorrected visual acuity, the numbers that I have heard right now sort of thrown out are 90 percent, 95 percent in the 20/25 to 20/30 range. I just want to know if there is some consensus on that distance visual acuity. Dr. Bradley?

DR. BRADLEY: Not sure.

DR. WEISS: Can we come up with a number for the agency as far as what we would consider efficacy for distance uncorrected visual acuity?

DR. BRADLEY: I think 100 percent better than 20/40.

DR. WEISS: A hundred percent better than 20/40. I personally would also like a higher level--it could be a lower percentage but a higher level of visual acuity and at least report the percentage, whether it is 20/25 or 20/30, or whatever. If 100 percent of people were 20/40 and

5 percent of people were 20/30 or better, I don't think any of us would consider this procedure efficacious. You are not that comfortable with it at 90 percent, 95 percent, 20/25, 20/30?

DR. BRADLEY: I think I would defer to the clinicians in the room dealing with patients. You have a sense of what they demand. I mean, the reason I think of 20/40 is that you need that to drive, and to take somebody who sees perfectly well with their spectacles and can drive, and then you give then a procedure to improve their refractive status and they can't drive is obviously a failure. That is one criterion I can be comfortable with.

DR. WEISS: Bill, you had suggested the 20/25, 20/30, 90 percent, 95 percent. Are you comfortable with that still?

DR. MATHERS: Yes, because I think that for driving you usually use both eyes. It is too stringent to say that 100 percent are going to be this because if you are coming from a plus 6 you might think your vision is a lot better even if that particular eye didn't quite get to 20/40 uncorrected and you are still going to be better off. So, 98 would be okay but I think 100 is too much.

DR. BRADLEY: You say 100 is too much but if you told the patients, by the way, 2/100 of your patients are no longer going to be able to drive after this procedure, nobody will have the procedure.

DR. WEISS: The agency wants to comment. After you comment I am going to ask you do you have enough--I know you don't have an answer from us but do you have enough information from us on this particular one because we are running behind? Yes?

DR. BLUSTEIN: Yes, 20/40 is just for an unrestricted driver's license. You can still drive with worse than 20/40.

DR. WEISS: Malvina, do you have enough information from us on this one? Enough information being established, the additional performance efficacy endpoints I think have already been discussed in terms of low contrast reading and maybe better driving function tests. If the agency is fine with that, we will go on with number 8, how do you recommend we evaluate patient's quality of life issue? I think a survey was mentioned. Does anyone have any additional ones? Dr. Eydelman?

DR. EYDELMAN: The question was specific to whether you can recommend a specific patient

questionnaire, not just do a patient questionnaire but can you go a step further and have any recommendations as to which one is appropriate?

DR. WEISS: There are three types of patient questionnaires on the screen, if anyone has any preferences as far as any of these go. Dr. Smith?

DR. SMITH: I am not going to express a preference for any outcome those specific questionnaires, however, I think it is important that refractive surgical type questions be in the questionnaire. All of those questionnaires don't include those types of questions. I think also the tasks that are being asked, some of them ask for specific tasks that are more specific for older individuals and the tasks that need to be asked about should certainly include driving and things that may be done by younger individuals.

DR. WEISS: And things that we have seen come before us already such as what percentage can read the newspaper without their glasses; what percent can read a restaurant menu, etc. without their glasses. Any other comments on this particular question? Dr. Rosenthal?

DR. ROSENTHAL: The two latter

questionnaires were done mainly for distance vision, and they were done early before near vision was considered a refractive surgical procedure. Does anyone have any information on near vision in the refractive surgical environment?

DR. BRADLEY: Certainly the impression I get from the silence around the table is that we are not familiar enough with these surveys but, clearly, you need to have questions that are going to assess near vision. You must have questions that are going to assess night vision and night driving. These are the obvious problems that these patients are going to experience. If these surveys do not include such questions you need to add them.

DR. ROSENTHAL: The surveys include a lot more about night driving and vision.

DR. WEISS: So, we need to add questions about reading. Dr. Smith?

DR. SMITH: Those questions then need to be validated. I mean, these are all validated questionnaires for distance.

DR. WEISS: Dr. Bressler?

DR. BRESSLER: I don't know about the NEI refractive but the NEI VFQ, visual function questionnaire, does include several questions to

get a subscale for near activities and it has been validated so that could perhaps be added to the ones you are looking at here.

DR. WEISS: The other thing is it may already include these but since the phenomena of the halos, star bursts and such seem to be a major side effect of these lenses, questions that address those also have to be in these surveys if they are not already. Dr. McMahon?

DR. MCMAHON: The one problem with using the VFQ for this is even though those questions exist, it was really designed for people who had poor vision so you would have substantial ceiling effects. That is where RQL actually was developed.

DR. WEISS: Well, I think you understand the sentiment, that this has to be more refractive surgery as opposed to diseased eye, and more set towards the younger as opposed to elderly individuals, with a lot of questions about visual quality and near vision. If there are no other comments on any--Dr. Bradley?

DR. BRADLEY: Finish your statement.

DR. WEISS: It was just if there are no other comments. I guess there are.

DR. BRADLEY: It doesn't really fit into

your questions but one issue I think that the FDA must address with these multifocal IOLs is how the patient is going to provide informed consent. I think this is not a trivial point with multifocal IOLs. How does the patient say yes, I agree to having multifocal optics when they have no idea what multifocal optics is; they don't understand the problems associated with multifocal vision? You cannot describe it to a patient and I wondered if the FDA had considered that. There are really two possibilities out there. Certainly one has been used. One is to provide the patient with simulated vision. I think Alcon did that with their Array lens. An alternative would be to have a sort of non-invasive version of multifocal optics provided to the patient, i.e., a contact lens. We saw that in our previous FDA panel meeting. That was for monovision. But, again, prior to the surgery can you provide the patient with some way so they can experience what multifocal optic vision is going to be like and, therefore, can provide informed consent? Because without the experience I am not sure they can actually provide informed consent.

DR. EYDELMAN: We actually tried to tackle

that problem and we recommended a couple of times multifocal contact trial before surgery. The problem is that not every MIOL design is paralleled exactly by the multifocal contacts. So, even though they will get a feel for what the multifocality might feel like, it won't be the same perception as when this is actually implanted. So, it is not a perfect solution.

DR. WEISS: You know, Arthur, there are things that we do to our patients every day that we can't really give them a full idea about.

DR. BRADLEY: Yes, but I am just a bit concerned. I think Dr. Maguire was alluding to this earlier, that a lot of these patients are not satisfied and want these lenses removed. I think that could have been avoided if they could have somehow seen what it was going to be like because this is a compromised vision situation, very clearly so.

DR. EYDELMAN: So, if your recommendation is for each sponsor to try to identify a multifocal contact lens which parallels the closest to their design, and to give the patients a trial--

DR. BRADLEY: Maybe a subgroup or something along those lines.

DR. EYDELMAN: Well, a subgroup won't solve your problem.

DR. WEISS: You know, Arthur, personally I think this is the problem you have in dealing with refractive surgery patients, to try to take out your bad candidates--which I assume the sponsor is going to want to do--up front because they are not going to want them filling out a survey saying they are dissatisfied when they can predict they were going to be dissatisfied no matter what happened. I think it is very hard to show the increased aberrations you have after LASIK. You can tell people about the quality of vision issues but it is hard to convey.

DR. BRADLEY: Yes, I agree and one last comment on that is Dr. Lane, who presented this morning, made a very clear statement. He said the clinicians want to provide, and I am quoting, true informed consent for this procedure. That is their goal, and he was sponsored by the IOL company so, clearly the IOL companies want this. The challenge is how do you do it.

DR. WEISS: That will be the last comment then. So, if the agency is fine with the answers to these questions, in the remaining few minutes we

have a second open public hearing session if there are any comments from industry. Mr. McCarley?

MR. MCCARLEY: I am just, again, sitting here as an industry person, I am trying to look at the companies that have a multifocal lens and want to have an accommodative IOL but also all of the others that simply have monofocal IOLs and I have looked at the literature also--correct me if I am wrong--most of the clear lens extractions up to now have been done with monofocal IOLs. So, we are looking forward. Why would we expect that to stop if they have other potential problems with multifocal lenses like potential degradation in optics and other issues? Why wouldn't I expect for a monofocal lens company to want to come in and try to treat presbyopia? In fact, today's title is clear lens extraction for the correction of presbyopia. Well, the correction of presbyopia, I believe, is done all the time, clear lens extraction just with the monovision. So, have we today addressed any of the issues for monofocal lenses or was today a multifocal lens discussion and an accommodative IOL discussion? Because that, to me at least so far, hasn't been the majority of clear lens extractions.

DR. WEISS: Dr. Eydelman?

DR. EYDELMAN: The goal of today was to focus on multifocal and accommodative IOLs.

MR. MCCARLEY: So, would you then expect to have a separate meeting with separate issues for monofocal lenses that are currently available in cataract surgery, treating presbyopia with monofocal lenses?

DR. EYDELMAN: Only if we find that we can't take the panel comments to the next step. In other words, we are going to meet internally when the situation arises and decide if we have the answers. If we don't, we might call a meeting; if we do, we will not.

MR. MCCARLEY: I would expect that occasion to arise very quickly if you have some companies wanting to do monofocal lenses. You know, they are easier to do studies on compared to multifocal lenses.

DR. WEISS: Does the agency have any other comments? Do panel members have any other comments? If not, I am going to ask Sally for concluding comments.

DR. EYDELMAN: We just want to thank the panel. It was a very clear and very concise

discussion. We appreciate it.

DR. WEISS: I don't think it was as clear and concise as your presentation but thank you anyway.

MS. THORNTON: I just want to, again, thank the panel and echo Malvina's sentiments. It has been a long day and I think we have gotten a lot out of your hard work, and I appreciate your time and attention to this issue. Thank you.

DR. WEISS: The open meeting is adjourned.

[Whereupon, at 3:52 p.m., the proceedings were adjourned.]

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